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Malignant Disease of the Uterus. A Digest of 265 Cases Treated in the New Hospital for Women.

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IN this paper we have collected the records of all the cases of malignant disease of the uterus which were treated in the wards of the New Hospital from 1895—1907. During these 13 years there were 217 cases in which the disease affected the cervix and 48 cases in which it affected the fundus.

Everyone who has undertaken an investigation of this sort will realize its difficulties and limitations. There is nothing more heart-breaking than to search for facts in old clinical notes, and when, to one's surprise and pleasure, they yield the necessary information, the pathological department is often at fault, and fails to supply a sufficiently good section to enable a definite diagnosis to be made in a doubtful case. Another difficulty arises from the fact that 15 years ago the importance of after histories was not realized as it is to-day, and while it is now the rule to write to or see all the post operative cancer cases at least once a year, they often used to be lost sight of when they left the hospital, so that in many of the early cases no history can be obtained beyond a sanguine, but not very helpful, note to the effect that " The patient returned home to-day, condition quite satisfactory."

In preparing this paper the clinical notes of all cases have been read, and all the microscopic sections that were available have been re-examined and reconsidered, in several instances where the diagnosis was doubtful and where the necessary material could be obtained, fresh sections having been cut. In more than one instance this has led to a revision of the original diagnosis.

No case has been included in the series unless its claim to malignancy was found to rest on a reliable pathological basis, or unless, in the advanced cases, the description of the local condition

or an after history of recurrence or death left no room for doubt. In considering the operation cases the test has been strictly pathological, and several cases have been discarded as doubtful although they were considered malignant at the time of operation and subsequently.

An attempt has been made to trace all the patients upon whom hysterectomy was performed, but the result, which will be found below, is far from complete owing to the fact that many of the letters were returned unanswered.

All the cases in this series have been under the care of various members of the staff of the New Hospital for Women, Euston Road, to whom we are indebted for advice and help on many points and for permission to use the clinical notes. Miss Cock, from the medical side of the hospital, contributes the only case of chorion-epithelioma, which she published as early as 1896 in the *British Medical Journal* as "A Case of Deciduoma Malignum with post mortem and microscopic appearances." The other cases have been under the care of the surgeons, Mrs. Scharlieb, Mrs. Boyd, Miss Aldrich Blake, Miss Chadburn and Miss Anderson. We also owe much to Mrs. Flemming and Miss Woodcock, who preceded Miss Platt as pathologists to the Hospital, and to whose careful investigations great interest attaches.

Unfortunately the notes of out-patient cases are not permanently kept, so that it is not possible to determine the ratio of cases in which radical removal of the uterus was attempted to the total number of cases coming to the hospital with malignant disease of the uterus.

Malignant disease of the CERVIX: Operative procedure.

In thirteen years changes have occurred in all branches of surgery, but perhaps in none more than in the special branch of pelvic surgery which we are considering. The operative procedure for dealing with cancer of the uterus has been transformed, a wide abdominal removal being substituted for vaginal hysterectomy, which in 1895 was the routine operation in our hospital as well as in other English hospitals. In the New Hospital abdominal hysterectomy for cancer of the cervix was first used in 1901, and since 1902 it has been the routine operation. The records of the cases of malignant disease of the cervix, in which hysterectomy was performed, show that in seven years, 1895—1901, the abdominal route was employed in two and the vaginal in twenty-five cases, whereas in the following six years, 1902—1907, 58 abdominal and only two vaginal hysterectomies were performed for the same condition. At first the operation of abdominal hysterectomy differed little from that done for fibroids or other non-malignant conditions, as no attempt was made to do a wide removal of the cellular tissue of the broad ligaments, but the technique has been gradually altered, until at the present time the

method is practically the same as that described by Dr. Kelly in his well-known text-book of operative gynæcology, *e.g.*, the removal of the uterus and appendages with the broad ligaments and the upper part of the vagina, the uterine arteries being divided well outside the line of the ureters. If the condition of the patient permits, a systematic search for and removal of the lymphatic glands in the base of the broad ligament, on the uterine artery and at the brim of the pelvis should be undertaken at the same time. In several of the more recent cases, the uterus has been isolated by the application of Wertheim's clamps before section of the vagina. The operation is finished by closing the pelvic peritoneum by a transverse suture, and the abdominal wound in the usual way, in three or four layers. The incision in the vaginal roof is left open and a temporary strand of gauze is passed through it in order to drain the large cellular space which is opened during the operation. When the gauze is withdrawn, 36 hours later, the cut edges of the vaginal wall fall together and, as a rule, firmly unite before the patient leaves the hospital in three weeks' time. This method of drainage has been modified in some of the recent cases, and the vagina only drained, but the results, so far, have not been favourable to such a change of procedure. There has been more tendency to cystitis, and in some of these cases blood clot has collected and cellulitis has occurred.

The importance of a thorough removal of the iliac and uterine glands, whenever possible, cannot be exaggerated. In the majority of cases in which there is recurrence, the metastasis is to be found in these glands, and as it is impossible to distinguish affected from non-affected glands at the time of operation, safety lies in their removal.

By the vaginal route, unless by very extensive section, it is impossible to remove the glands or even the cellular tissue of the broad ligaments to more than a limited extent. The fact that certain cases have succeeded after a high amputation of the cervix, or a vaginal hysterectomy, is no justification for the use of these operations. An enormous weight of evidence shows that the narrower the removal, the greater is the danger of leaving infected cells behind, and although it is impracticable to remove the whole lymphatic system draining the uterus, to the same extent that it is for the breast, we should approximate as closely as possible to the ideal treatment which, in the present state of our knowledge of cancer, is complete extermination of the diseased organ and the lymphatics draining it.

At the present time it is scarcely necessary to put forward arguments in favour of the abdominal route as they have been accepted by the great majority of gynæcologists in England and abroad, but as the abdominal operation was used in the New Hospital

before its general adoption in English hospitals the comparison between our two series of cases may be of some interest.

Everyone recognizes that abdominal hysterectomy for cancer is a grave operation, difficult to perform and causing considerable shock to the patient, but it is also fair to remember that in experienced hands the primary mortality is not very high and that it is falling.

In the New Hospital cases the primary mortality for abdominal hysterectomy is 6·6 per cent. (*i.e.*, six deaths having occurred within a week of the operation out of a total of 90 cases who were operated upon), and 7·3 per cent. for vaginal hysterectomy (*i.e.*, three deaths, two on the operating table and one of septic peritonitis, out of a total of 38 cases operated upon).

If it is remembered that, in the calculation of this mortality rate, all deaths from abdominal hysterectomy (for cancer) are included, early cases as well as recent ones, and if it is also borne in mind how much the scope of operation has been extended by the use of the abdominal route, a radical removal being now attempted in much more advanced cases than was possible with vaginal hysterectomy, the comparison between these figures becomes more striking, and it certainly does not tell against the abdominal method.

After vaginal hysterectomy patients used commonly to die from local recurrence in the vaginal vault. The first sign of trouble often took place very soon after the operation. Out of the total number of cases—29—in which vaginal hysterectomy was done for cancer of the cervix, the disease recurred in twelve cases in the vaginal scar within a few weeks from the time of the operation.

After abdominal hysterectomy, as it is now done, it is exceptional to have a local recurrence, and with increasing operative skill and the use of Wertheim's clamps in suitable cases, it is reasonable to hope that the number will be further reduced. In the whole series of abdominal hysterectomies for cancer of the cervix, comprising 58 cases, local recurrence has taken place in four or possibly five patients, three of whom were among the earliest in the series.

After a complete abdominal pan-hysterectomy metastasis, if it occurs, is most likely to affect the iliac glands. Hence the importance of their removal at the time of operation if possible. By the naked eye there is no way of discriminating between affected and unaffected glands. Small glands may contain cancer cells, and large ones may be simply inflammatory. This being so, it is obvious that an effort should be made to remove *all* accessible glands at the primary operation. In bad cases it is no light matter to undertake a systematic search for glands at the end of a long operation, and even in those cases in which it seems as if satisfactory removal had been accomplished the patient may develop symptoms of internal recurrence a year or two later.

The number of patients in our series who have returned about two

years after their operation with symptoms due to recurrence in the iliac glands is very striking, and, it must be admitted that, there is little hope of successfully removing these glands at a secondary operation if this is undertaken when the glands are large enough to be felt on abdominal palpation, or when the patient herself is conscious of symptoms for which they are responsible. Until the glands become adherent to the iliac vessels and other structures they do not cause symptoms, and when they have become adherent, the time for their removal has passed. This fact was demonstrated in several of our patients in whom secondary operations were performed on account of pain, discomfort or palpable swelling in the region of the iliac glands.

In this connection, it may be of interest to refer to a patient who returned to the hospital three years after hysterectomy, on account of a ventral hernia. Except for the discomfort of the hernia she considered herself to be in perfect health. When the abdomen was opened for repair of the hernia Miss Aldrich Blake took advantage of the opportunity to remove the iliac glands. They had caused no symptoms, but upon microscopic examination they showed deposits of cancer cells. It is now more than a year since the second operation, and over four years since the hysterectomy, and the patient is in perfect health. This interesting case led Miss Aldrich Blake to suggest whether it would not be well to advise an exploratory laparotomy, irrespective of symptoms, eighteen months or two years after hysterectomy for cancer of the cervix. The risk incurred from an exploratory operation is slight, and the advantage to be derived from it might be great.

Comparison of the after results of abdominal and vaginal hysterectomy is instructive.

Of the 29 patients upon whom vaginal hysterectomy was performed for cancer of the cervix, one is known to be alive and well at the present time, seven years after the operation. The malignancy of this case has been subjected to close scrutiny, especially as the note on the condition of the cervix and the description of the parts which were removed at the operation by no means carry conviction. The entry in the clinical notes is Mrs. B., æt. 38, 1901, slide No. 675,673: "Uterus small, good position, quite movable, cervix large and thickened, bleeds on examination. There are nodular growths about the os." This description would do for an unhealthy cervix with erosion and distended Nabothian follicles. A further entry in the clinical record goes on to say that at a second examination the cervix did not bleed, and that Mrs. Boyd, to whom the case belonged, considered it doubtful whether it was or was not malignant. A small piece of tissue was removed from the cervix and a frozen section examined. It was reported to be early squamous

celled carcinoma, and the uterus was removed. The section to which we are fortunately able to refer supports the original diagnosis of malignancy. If the case is accepted as a genuine one of cancer of the cervix, it is an example of a remarkably good result following vaginal hysterectomy in what obviously was an early case. Two cases, which were respectively an endothelioma and squamous celled carcinoma, remained well for two years, in 12 the disease recurred very soon after the operation, and the other patients have been lost sight of.

The results from abdominal hysterectomy cannot be regarded as good, but they are very much better than the tragic figures which we have just quoted. The after results of 58 abdominal hysterectomies for cancer of the cervix are as follow:—

26 patients are known to be alive and well at the present time, between $1\frac{1}{2}$ and 4 years after their operations.

17 patients developed symptoms of recurrence, 11 cases in the first year and 6 cases within $3\frac{1}{2}$ years after their operations.

15 patients cannot be traced.

Malignant disease of the FUNDUS.

It is well recognized that this is a much more hopeful condition. The lymphatics are not affected until late, so that in the removal of the uterus an extensive dissection of the cellular tissues of the broad ligaments is not required, and there is every hope that a comparatively early operation will result in permanent cure.

Of the 48 patients suffering from malignant disease of the fundus 39 were treated by hysterectomy, 9 by vaginal and 30 by abdominal hysterectomy. The after histories of these 39 cases compare very favourably with those of cancer of the cervix:—

22 patients have remained in perfect health since the operation, which was performed at varying intervals of 2—7 years ago.

7 patients developed symptoms of recurrence, from 1—5 years after hysterectomy.

3 patients died.

7 patients cannot be traced.

ANALYSIS OF CASES: Pathological Classification.

Cervix, 216 cases. Of these, 93 were squamous-celled carcinoma; 24 were adeno-carcinoma; 93 were of unspecified variety; 2 were sarcoma; 4 were endothelioma.

Fundus, 48 cases. Of these, 37 were adeno-carcinoma; 1 was chorion-epithelioma; 10 were sarcoma.

Of the 48 fundus cases, 17 were associated with fibroids, while of the 216 cervix cases in only 4 were fibroids noted as present.

In classifying these malignant tumours of the uterus, for the most part easily grouped, we found in a few instances some difficulty

in placing them in their respective classes. Many of the earlier cases were incompletely reported upon; for instance, tumours of the cervix were described as carcinomata, no distinction being made between squamous-celled and adeno-carcinomata. As, unfortunately, no sections of these tumours were available for further examination, they have been grouped together in one class—unspecified or doubtful. All other reports have been verified by reference to the microscopic sections.

Tumours of the CERVIX:

Squamous Carcinoma or Epithelioma of the Cervix. By far the greater number of our specimens of carcinoma of the cervix are of the squamous-celled variety. This fact does not support the statement made by Roberts in his *Outlines of Gynæcological Pathology*, to the effect that the common type of cancer affecting the cervix appears to be a columnar-celled glandular carcinoma.

Our series of microscopic sections serve to illustrate the three varieties of epithelioma described by Lazarus Barlow. Some of them, arising apparently from the Malpighian layer of the epithelium, show in places masses of cells arranged in layers round a central space, giving somewhat the appearance of a tubular growth. The peripheral cells have in a lesser or greater degree the characters of germinal epithelium, being columnar in shape, and taking nuclear stains well. As the cells approach the lumen they tend to become compressed, and approach the keratinous type. In the lumen itself may be seen débris of cells, pieces of keratinous material and remnants of stroma. Rapidly growing tumours of this variety in which the cells show little differentiation from their original type, and no keratinization, may easily be mistaken for glandular carcinoma. Another variety possibly arising from the prickle cell layer is one which is composed mainly of polyhedral or rounded cells, which show vacuolation or separation of the nucleus from the body of the cell. Other tumours have well-marked cell nests, with cells containing keratin. Several of our specimens have numerous cell nests. Evidently the presence of these in epitheliomatous growths of the cervix is not as rare as has been thought. It is surprising in how many cases careful search in microscopic sections is rewarded by the finding of one or more well-defined whorls. The discovery of an undoubted cell nest has, on more than one occasion, determined the inclusion among the epitheliomata of a tumour which might otherwise have been described as columnar carcinoma.

Adeno-carcinoma of the Cervix. These growths, originating from the columnar epithelium of the cervical glands, have the main characteristics of the carcinomatous tumours of the fundus, as described later. In several sections taken from the growing edge of the tumour, the basal position of the nucleus, typical of the cervical columnar cell, is well seen.

Some of the specimens present difficulty in diagnosis, in that the glandular mode of growth is lost sight of, and the cells, owing to pressure, have lost their columnar shape, becoming rounded or polyhedral, thus simulating an epithelioma. Sections taken from the growing edge will often clear up the difficulty.

Sarcoma of the Cervix. These are quite typical cases, and easily diagnosed.

Other Mesoblastic Tumours of the Cervix. Among the specimens are several in which diagnosis has presented many difficulties. These tumours, microscopically examined, seem to possess many of the characters ascribed to malignant growths which have their origin in the endothelial lining of lymphatics or blood-vessels.

It has been said that in the present unsatisfactory state of our knowledge of the characteristics of endotheliomata, it is not justifiable to diagnose such a tumour unless the transition from normal endothelium to tumour endothelium can be demonstrated. In no one of our cases can this be done, but in some of them the microscopic appearances strongly suggest endothelioma. It is true that in many points there is also a resemblance to the Malpighian type of squamous epithelioma, and it is possible that in one or more of the cases the tumours may be of this variety, but after due consideration it has been considered allowable to include four of the cases in the class of endotheliomata.

Case I. K.T., æt. 18, was reported upon by the pathological committee of the Obstetrical Society, *Trans. Lond. Obst. Soc.*, vol. xlvii, p. 320. A brief description of the other three cases is given below.

Case II. Mrs. H., æt. 41, 1905, slide No. 256, etc. Sections of the primary growth, taken from different parts, show strings or columns of cuboidal cells. Running parallel with these and outside them are several layers of fibrous tissue. Some of the columns are canalized, showing definite lumina. The sections pass through them in varying directions, some being transverse, others oblique and others longitudinal. The rounded ramifications of the strings of cells are characteristic and are hardly to be mistaken for the more angular growth of ordinary carcinomatous cells in lymphatic spaces. The individual cells are small and have well-defined rounded nuclei which do not take the stain quite as well as the nuclei of carcinomatous cells. In the sections of secondary growths in glands the same arrangement of the cells is apparent, though not so marked, and the cells vary greatly in reaction to stain, and in size, some of them being enormous, others quite small.

Case III. Mrs. W., æt. 52, 1900, slide No. 592, etc. Unfortunately this case is only represented by unsatisfactory sections. They show well-defined blood spaces, surrounded by irregularly disposed

cuboidal or low cylindrical cells, those nearest the lumen being well-formed and suggestive of endothelium. Between these columns of cells run bundles of fibrous tissue.

Case iv. Mrs. W., æt. 33. 1905, slide Nos. 447, 715, etc. The growth in this case was confined entirely to the cervix, above it was a mass of polypoid endometrium. The sections, as in the specimen first described, show interlacing strings or canalized columns of round or cylindrical cells. In places the cells are in masses, and are separated by a thin fibrillary intercellular substance. In the fibrous tissue between the cell groups is a good deal of small round-celled infiltration. The appearance of the columns of cells does not in any way suggest columnar-celled carcinoma, having a much greater resemblance to sarcomatous tissue.

Tumours of the FUNDUS: Adeno-carcinomata.

The carcinomatous tumours of the fundus consist entirely of adeno-carcinomata, of which all varieties are present. We have not been fortunate enough to find any specimen of squamous-celled carcinoma, though in at least one case the columnar type of epithelium is quite lost, and the growth in many respects resembles squamous carcinoma. The adeno-carcinomata vary greatly in both their cellular and glandular structure. In some, the characteristics of malignancy are confined almost entirely to the glands, the epithelium being fairly well formed, and mostly in a single layer, while the basement membrane is intact. The glands show riotous overgrowth, becoming tortuous, and losing their glandular shape. Tumours of this type have been considered as of doubtful malignancy, especially as, in many cases, the growth does not penetrate deeply into the muscular coat. A curetting is not always satisfactory as a means of diagnosis in these cases, in that a section of hyperplastic endometritis may bear a strong resemblance to the so-called adenoma malignum; also, in tissue from a curetting, of course, one does not expect to find evidence of penetration into the muscular coat, though this if only superficial, and taken alone is not enough to establish a diagnosis of malignancy, as in sections of a normal uterus one may sometimes see glands surrounded by the more superficial muscular fibres. It is rare, however, in a microscopic section of a curetting of a uterus, in which this type of growth is present, not to find some definite signs of malignancy. The character of the epithelium, its staining reaction, direction of the axes of the nuclei, the presence or absence of the basement membrane, should all be carefully considered, and we cannot urge too strongly the importance of recognizing these cases early, and not waiting till the disease is too far advanced for satisfactory treatment.

Other cases in which the diagnosis is quite simple are those in which the glands have become irregularly multi-layered, the cells

having the characteristics of malignant cells and the basement membrane being lost. In places the lumina of the glands are quite obliterated, and the growth has deeply invaded the muscular wall of the uterus.

Chorionepithelioma of the Uterus.

The one case of this variety of tumour has the characteristic microscopic appearance of a chorionepithelioma. The sections show well-marked cells of the Langhans type, with masses of syncytium.

Sarcoma of the Fundus.

The 10 specimens of sarcoma are of the round, spindle or mixed-celled varieties.

Fibro-myomata in Conjunction with Malignant Tumours.

It is interesting to note the large proportion of cases of cancer of the endometrium, which were accompanied by fibroids in the uterine wall. Out of 37 cases of adeno-carcinoma no less than 17 of the uteri contained fibroid tumours, and of 10 cases of sarcoma 4 had fibroids. The high proportion of cases, in which malignant disease of the fundus and fibroids co-exist, suggests a causal relation between the two conditions.

It is obviously impossible to determine the proportion of women in the ordinary adult female population who have fibroids, but judging from examination of patients in the gynæcological out-patient department, among whom fibroids would tend to be of more common occurrence than in ordinary women of the same age, the number having fibroids falls very much below 1:3, which is the ratio in which fibroids were present in our cases of cancer of the fundus. These figures suggest that it is necessary to regard all fibroids with suspicion and to advise their close supervision and their removal as soon as they cause symptoms.

It is undoubtedly a fact that in the majority of cases of fibroids, especially of the submucous or interstitial variety, a hyperplastic endometritis is present. Whether the two conditions are due to some common cause, to be found in elderly spinsters who are the class most liable to both diseases, or whether the endometritis is occasioned by some process of irritation of which the fibroid is the source, is a matter for investigation. A systematic microscopic examination of the endometrium in all cases of fibroids, might possibly throw light on the matter.

In some of the cases of sarcoma with fibroids, of which there were four, the diagnosis was difficult. In deciding on the malignancy of such a tumour, stress must be laid on the irregularity in size and staining of the nuclei, the presence of mitoses and the passage to quite irregular forms.

Degree of Malignancy.

The New Hospital cases are in accordance with the following recognized facts, that cancer of the cervix is enormously more malignant than cancer of the fundus, and that it occurs in younger women and in those who have had children.

Sarcoma of the uterus, especially sarcoma of the cervix, appears to be particularly malignant. Sarcoma of the fundus is not nearly as rare as sarcoma of the cervix.

Age Incidence and Fertility.

The analysis of the ages and social condition of the patients corroborates the results of previous investigation. The vast proportion of women with cancer of the cervix are over 30 and have had children while the great majority of those with cancer of the fundus are over 50 and have not had children, but there are exceptions to both rules. Women under 30 may develop cancer of the cervix and similarly the mothers of large families may suffer from cancer of the fundus. Sterility and virginity do not absolutely protect from one form of cancer any more than fertility does from the other.

Of the total number of women in our series who suffered from cancer (in distinction to sarcoma) of the uterus, the cervix was affected in 215 and the fundus in 38 cases. In the *cervix* cases, the average age of the patients was 44·5 years, and the average number of children per patient was five, while 107 women (50 per cent.) had had five or more children. Only six of these patients were unmarried and childless. In the *fundus* cases, the average age was 58 years, and the average number of children per patient was one, while only three of them had had more than five children. Eighteen of these women, or nearly half the whole number, were unmarried and childless.

If the cases are studied by taking the ages in decades it is shown that cancer of the cervix tends to occur in women who are about ten years younger than those affected with cancer of the body. Sarcoma of the fundus is less uncommon in young and married women than carcinoma.

Incidence of disease—arranged by taking the ages in decades.

Ages of Patients.	Carcinoma of the Cervix.	Carcinoma of the Fundus.	Sarcoma of the Fundus.
20—30 years	6	0	1
30—40 ,,	45	0	2
40—50 ,,	80	7	3
50—60 ,,	48	17	2
60—70 ,,	18	11	2

A closer investigation of the patients under 30 years of age who suffered from malignant disease of the cervix shows that the two youngest, who are the only ones not included in the table which has just been given, aged 15 and 18, were cases of mixed cell sarcoma and endothelioma.

The others were of varying ages up to 30, all were married women, and with one exception all had had at least one child. In young patients the disease showed a high degree of malignancy, and either proved to be inoperable when first seen or recurred within a year after removal of the uterus. It is perhaps worth while to notice that the girl with sarcoma of the cervix, aged 15, had been treated for some months in the gynæcological department of a London hospital. She complained of vaginal discharge but no pelvic examination was made until admission, when the vagina was found to be distended by a huge fungating growth. This case emphasizes the importance of making a thorough local examination even in young girls, under anæsthesia if necessary.

In our series there are 5 cases of cancer of the cervix in virgins of mature years, between the ages of 37 and 48. These patients had not worn pessaries and no cause of local irritation could be found. The hymen was noted to be intact in all. Three were examples of squamous cell carcinoma, one of adeno-carcinoma, and one was doubtful.

We hoped to form some conclusions in regard to the symptomatology of the disease, but we can only give a colourless statement of facts that are already well known.

In the great majority of the cases symptoms were absent until late in the disease, and in all the cases of cancer of the cervix *pain was the last symptom of which complaint was made.* In cancer of the fundus the order in which symptoms developed was: discharge was the first symptom in 17 cases, hæmorrhage in 10, pain in 2. Of the 10 cases of sarcoma of the fundus, hæmorrhage was the most marked or the only symptom in 6 cases.

In conclusion we should like to express our hesitation in offering this small contribution to the already overburdened literature which deals with the subject of cancer of the uterus. It contains nothing new, and it only represents a record of cases which have been investigated as thoroughly and carefully as the circumstances permitted.